has now rejected all pending claims under 35 U.S.C. § 112, first paragraph, as not enabled and failing to satisfy the written description requirement.

Applicants respectfully traverse these rejections with respect to all pending claims for the reasons discussed below.

Rejection under 35 U.S.C. § 112, first paragraph, as failing to meet the enablement requirement

The Examiner has rejected claims 5 to 32 under 35 U.S.C. § 112, first paragraph, as non-enabled. In particular, the Examiner alleges that at the time of filing of the instant application the state of the art in finding inhibitors of the replication of the hepatitis C virus (HCV) was unpredictable, that one of ordinary skill in the art would not accept such a therapeutic regimen on its face, that screening data showing that the instant compounds inhibit the function of the HCV polymerase enzyme is not sufficient to enable the instant compound claims, that there is no evidence of "functional treatment" in humans, and that the pharmacological activity of the claimed compounds cannot be predicted from their structure. Based on all of these factors, the Examiner concludes that because Applicants allegedly have not provided sufficient guidance to one of ordinary skill in the art regarding how to use the claimed compounds, the instant claims do not meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

The enablement requirement provides that claims are sufficiently enabled if one of ordinary skill in the art could make and use the claimed invention without undue experimentation. Further, the Federal Circuit has indicated that the utility requirement of 35 U.S.C. § 101 is also a component of the enablement requirement. See In re Ziegler, 992 F.2d 1197 (Fed. Cir. 1993). Where the application at issue claims compounds per se and bases the utility of such compounds on a pharmacological activity, the Federal Circuit has clearly delineated the procedure an Examiner must follow in making a rejection under either § 101 or § 112, first paragraph, for lack of utility. See In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995). In Brana, both the Examiner and the Board rejected applicants' compound genus claims under 35 U.S.C. § 112, first paragraph, on the basis that the compounds lacked utility. On appeal, the Federal Circuit reversed the decision of the Board, finding that applicants had provided sufficient *in vitro* and *in vivo* test data for the claimed compounds to meet the utility requirements of both §§ 101 and 112.

In their discussion of the claims at issue in Brana, the court enunciated a two-part procedure with respect to determining whether claims directed to compounds per se meet the utility requirement. First, the applicant must have alleged a "sufficiently specific use" for the compounds. Id. at 1555. Second, the Examiner then has the burden to challenge this presumptively correct assertion of utility by providing "evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." Id. at 1566 (emphasis added); see Ex parte Rubin, 5 U.S.P.Q. 2d 1461, *5 (BPAI 1987) (". . . a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility

requirement for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.'") (quoting In re Langer, 503 F.2d 1380 (CCPA 1974)). Such evidence must tend to show that the claimed invention relates to an "inherently unbelievable undertaking or involve[s] implausible scientific principles." In re Brana, 51 F.3d 1566 (emphasis added). Providing the Examiner has met this burden, only then does the burden shift to the applicant to provide rebuttal evidence in support of the invention's asserted utility. Id.; In re Bundy, 642 F.2d 430, 433 (CCPA 1981) ("The PTO must have adequate support for its challenge to the credibility of applicant's statement as to utility. Only then does the burden shift to appellant to provide rebuttal evidence.").

Applicants respectfully submit that they have satisfied the enablement requirement of 35 U.S.C. § 112, first paragraph, and traverse the rejection with respect to all pending claims for at least the following reasons: (1) Applicants have alleged a sufficiently specific, practical utility for the instantly claimed compounds that is neither implausible nor inherently unbelievable; (2) the Examiner has not met the PTO's burden of demonstrating that the instantly claimed compounds lack utility by providing evidence that one of ordinary skill in the art would reasonably doubt the asserted utility, and has therefore improperly shifted the burden of proof to Applicants to demonstrate such utility; and (3) the Examiner has required Applicants to provide a greater quantum of evidence regarding the utility of the presently claimed compounds than is required under either 35 U.S.C. §§ 101 or 112, first paragraph. Each of these points is discussed in turn below.

1. Applicants have alleged a sufficiently specific, practical utility for the instantly claimed compounds that is neither implausible nor inherently unbelievable

Applicants' originally-filed specification states that the instantly claimed compounds have a specific and useful pharmacological activity, inhibition of the HCV polymerase enzyme. Such inhibition is useful in preventing replication of the HCV virus in HCV-infected cells. This inhibition of HCV replication in cells is useful for treating HCV infections in HCV-infected mammals, such as humans. See, for example, page 1, lines 7 to 9; page 23, lines 6 to 34; page 495, lines 16 to 19; and page 495, line 28 to page 513, line 5.

This statement of utility is sufficiently specific and practical to meet the first part of the two-part test enunciated by the Federal Circuit in Brana. As such, Applicants respectfully submit that they have met the first test of Brana and the burden is on the Examiner to provide evidence that this utility would be doubted by one of ordinary skill in the art. See Fujikawa v. Wattanasin, 93 F.3d 1559, 1564 (Fed. Cir. 1996) (stating that "in the pharmaceutical arts, our court has long held that practical utility may be shown by adequate evidence of any pharmacological activity").

Furthermore, Applicants also provide *in vitro* data demonstrating that the claimed compounds possess activity as inhibitors of the HCV polymerase enzyme. In particular, the testing data found on pp. 495 to 513 of Applicants' specification, coupled with the knowledge in the art at the

time the application was filed, would have provided enough evidence to convince one of ordinary skill in the art of the asserted utility. See Nelson v. Bowler, 626 F.3d 853, 856 (CCPA 1980) ("tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use").

The knowledge in the art at the time of filing of the instant application with respect to the asserted utility of interfering with the functioning of the HCV polymerase enzyme as a means of inhibiting the replication of the HCV virus is evidenced by the scientific article cited by the Examiner in the instant Office Action (S.L. Tan et al., "Hepatitis C Therapeutics: Current Status and Emerging Strategies," *Nature Reviews, Drug Discovery* (2002), Vol. 1, pp. 867 to 881). In particular, the article points out that it was understood as of 2002 that the HCV polymerase enzyme (also referred to as the "HCV NS5B polymerase" or "RdRp" enzyme) was a "validated target for antiviral therapy in that its activity is essential for HCV viral replication and infectivity in a chimpanzee model." Tan et al., p. 874, lines 1 to 4 (emphasis added). Furthermore, it was understood at the time that a small molecule called "JTK-003," an inhibitor of the HCV polymerase enzyme, was undergoing clinical trials for the treatment of HCV infections in humans. Tan et al., pp. 874 to 875. Therefore, one of ordinary skill in the art at the time of filing of the instant application would have understood that there was a reasonable correlation between inhibition of the function of the HCV polymerase enzyme and *in vivo* inhibition of replication of the HCV virus. Such a reasonable correlation is all that is required to satisfy the utility requirement for compound claims under either 35 U.S.C. §§ 101 or 112, first paragraph. See Fujikawa, 93 F.3d at 1564 (to establish practical utility, "there must be a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, that the novel compound will exhibit the asserted pharmacological behavior"); Cross v. Iizuka, 753. F.2d 1040, 1050 (Fed. Cir. 1985) (where the Federal Circuit held that *in vitro* test results were sufficient to satisfy the utility requirement because there was a reasonable correlation between the *in vitro* and *in vivo* activity of the claimed compounds); Manual of Patent Examining Procedure 8th Edition, Rev. 3, §2107.03, pg. 2100-44 (USPTO August 2005) ("If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays . . . will be sufficient to establish . . . pharmacological utility for a compound. . .").

Furthermore, the Examiner alleges that the instant compound claims are not enabled because one of ordinary skill in the art could not predict the pharmacological properties of the compounds because they are not structurally similar to known compounds having the same activity. Office Action, p. 4, lines 6 to 8. Applicants respectfully point out that there is no need for one of ordinary skill in the art to predict the pharmacological properties of the claimed compounds on the basis of structural similarity to known inhibitors of the HCV polymerase enzyme because screening data evidencing such activity against the HCV polymerase enzyme is provided at pp. 495 to 513 of the originally-filed specification.

For these reasons alone, Applicants respectfully submit that the instant claims are sufficiently enabled and ask that the Examiner withdraw the present rejection.

2. The Examiner has not met the PTO's burden of demonstrating that the instantly claimed compounds lack utility by providing evidence that one of ordinary skill in the art would reasonably doubt the asserted utility, and has therefore improperly shifted the burden of proof to Applicants to demonstrate such utility

As discussed above, the Federal Circuit has clearly delineated the procedure an Examiner must follow in making a rejection under either § 101 or § 112 for lack of utility where the application at issue claims compounds per se and bases the utility of such compounds on a pharmacological activity. When the applicants have alleged a sufficiently specific, practical utility, the Examiner has the burden of challenging such a presumptively correct assertion of utility. To make such a showing, the Examiner is required to provide specific evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. In re Gaubert, 524 F.2d 1222, 1224-25 (CCPA 1975) ("Accordingly, the PTO must do more than merely question operability, it must set forth factual reasons which would lead one skilled in the art to question the operative truth of the statement of operability."). Such evidence must tend to show that the claimed invention relates to an "inherently unbelievable undertaking or involve[s] implausible scientific principles." In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

In this case, the Examiner has not met this burden because no evidence has been proffered showing that one of skill in the art would reasonably doubt the asserted utility of the claimed compounds, the inhibition of HCV replication by inhibition of the HCV polymerase enzyme. As such, the Examiner has improperly shifted the burden of proof in requiring that Applicants provide additional evidence in support of the stated utility.

Specifically, the Examiner has simply stated that there is no "absolute predictability" in determining which compounds exhibit the desired specific pharmacological activities. Office Action, dated August 19, 2005, p. 3, lines 1 to 6. Based on this alleged uncertainty, the Examiner simply concludes that these obstacles establish that one of ordinary skill in the art would not accept any therapeutic regimen on its face. Id. Such a bald conclusion, unsupported by specific evidence, is not sufficient to meet the burden of proof enunciated by the Federal Circuit in Brana. See In re Gardner, 475 F.2d 1389, 1392 (CCPA 1973) (Court reversed the Board's finding of no utility because the Patent Office showed inadequate support for its doubts about the asserted utility). In particular, the Examiner has failed to point to specific evidence showing that one of ordinary skill in the art, reading Applicants' specification and taking into account the test data provided at pp. 495 to 513, would reasonably doubt Applicants' asserted utility on its face. The Examiner has pointed to no evidence showing that one of ordinary skill in the art would consider the asserted utility as an "inherently unbelievable undertaking" or that the inhibition of HCV replication by interfering with the

functioning of the HCV polymerase enzyme relies on "implausible scientific principles." In fact, as indicated above, those of ordinary skill in the art believe that the HCV polymerase enzyme is a "validated" and attractive target for developing treatments for mammals infected with the HCV virus.

As such, the Examiner has not met the initial burden of demonstrating that the instant claims relate to an invention with no practical utility. Therefore, the Examiner has improperly shifted the burden to Applicants to provide proof of the asserted utility. For this reason alone, Applicants respectfully ask that the rejection be withdrawn.

3. The Examiner has improperly required Applicants to provide a greater quantum of evidence regarding the utility of the claimed compounds than is required under either 35 U.S.C. §§ 101 or 112

Next, Applicants respectfully submit that the Examiner has improperly required Applicants to provide a greater quantum of proof regarding the utility of the claimed compounds than is necessary to satisfy the statutory requirements of either 35 U.S.C. §§ 101 or 112, first paragraph. In particular, the Examiner stated that the enzyme inhibition data provided in Applicants' specification "does not provide sufficient operational guidance in an 'individual' in patho-physiological environment [sic]." Office Action, p. 3, lines 13 to 15. Further, the Examiner asserted that such data is insufficient because there is no evidence of "functional treatment, i.e. no correlation to treatment in humans." Id. at lines 16 to 17. Last, the Examiner states that "more than mere assertions or screening data is needed unless one of ordinary skill in the art would accept the utility statement as obviously valid and correct." Id., p. 4, lines 3 to 5. Applicants submit that the types of data required by the Examiner in this case is not required to satisfy the utility requirement of 35 U.S.C. § 101 or the enablement requirement of § 112, first paragraph, for claims to compounds. See In re Langer, 503 F.2d 1380, 1392-93 (CCPA 1974) ("It is not proper for the Patent Office to require clinical testing in humans to rebut a prima facie case for lack of utility when the pertinent references which establish the prima facie case show *in vitro* tests . . ."); Manual of Patent Examining Procedure 8th Edition, Rev. 3, §2107.03, pg. 2100-45 (USPTO August, 2005) ("Office personal should not impose on applicants the unnecessary burden of providing evidence from human clinical trials.").

The issue of whether *in vitro* data is sufficient to meet the utility requirement for compound claims was squarely faced by the Federal Circuit in Cross v. Iizuka, 753 F.2d 1040 (Fed. Cir. 1985). In that case, Appellants argued that the *in vitro* data contained in Appellees priority document was insufficient to support the stated utility and, therefore, Appellees were not entitled to the benefit of their earliest filing date. The Board disagreed with Appellants and instead found that such data satisfied the utility requirement because the application was directed to a specific utility and the *in vitro* activity was reasonably correlated with an *in vivo* activity. The Federal Circuit affirmed the Board's decision and further stated that a "rigorous correlation" between an *in vitro* utility and *in vivo* activity is not required where the disclosure of an *in vitro* pharmacological activity is "reasonable

based upon the probative evidence." Id. at 1050. Eleven years later, the Federal Circuit in Fujikawa again found *in vitro* data alone enough to establish practical utility because the evidence showed that *in vivo* activity is typically highly correlatable to a compound's *in vitro* activity in this field. 93 F.3d at 1565.

Furthermore, in Brana, the Federal Circuit specifically rejected an argument that more than preclinical testing is necessary to show that claimed compounds possess sufficient utility. In this respect, the court stated "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws." 51 F.3d at 1568 (citing Scott v. Finney, 34 F.3d 1058, 1063 (Fed. Cir. 1994)). Instead, the court recognized that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." Id. The court endorsed the policy of encouraging early disclosure of compounds having important pharmacological properties:

> Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Id. Moreover, in In re Bundy, the Court of Customs and Patent Appeals recognized the same public policy issue and specifically rejected an argument that an applicant should have to provide *in vivo* data for every species included in a genus claim in order to satisfy the utility requirement for such a genus. 642 F.2d at 434.

Additionally, the Courts recognize that there is a distinction in the enablement standard with regard to claims drawn to compounds and those drawn to methods of treating diseases in humans by administering such compounds to those in need. It is clear that, with respect to compound claims, all that is necessary to satisfy the utility requirement is knowledge of some pharmacological activity of the compounds coupled with a knowledge as to the practical application or use of this activity. See In re Bundy, 642 F.2d at 434; In re Gardner, 475 F.2d 1389 (CCPA 1973). Furthermore, it is clear that *in vitro* test data constitutes a "pharmacological activity" that may demonstrate a practical utility in satisfaction of the requirements of §§ 101 and 112. See Cross, 753 F.2d at 1048 ("The stated utility . . . is directed to a specific pharmacological activity . . . the inhibition of thromboxane synthetase *in vitro*."); and Nelson, 626 F.2d at 856 ("the board erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use.").

In the instant case, Applicants have provided *in vitro* test data for many species falling within the claims at issue, showing that they are active inhibitors of the HCV polymerase enzyme. As discussed earlier, at the time of filing of the instant application, the HCV polymerase enzyme was recognized by those of ordinary skill in the art as a "validated target" for the therapeutic treatment of humans infected with the HCV virus. Therefore, Applicants respectfully submit that they have made

a sufficient showing in support of the asserted practical utility for the compound claims at issue by providing screening data showing that the claimed compounds are active as inhibitors of the HCV polymerase enzyme target.

Finally, public policy encourages inventors to file early applications with disclosures containing *in vitro* test data, without lengthy waits to generate *in vivo* data. See Cross, 753 F.2d at 1051 ("Successful in *vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public. . ."). Early filing of such applications puts scientific information into the public domain, therefore benefiting the public through the early dissemination of such information. See Nelson, 626 F.2d at 856 ("It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities."). Also See In re Bundy, 642 F.2d at 434 ("Requiring specific testing of the thousands of prostaglandin analogs encompassed in the present claim in order to satisfy the how to use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public."); In re Brana, 51 F.3d at 1568 ("Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue potential cures in many crucial areas. . ."). Therefore, Applicants respectfully submit that public policy requires that *in vitro* data that provides a reasonable correlation to an *in vitro* pharmacological property is sufficient to satisfy the practical utility requirement of §§ 101 & 112. Applicants have provided such data in the instant disclosure and, therefore, respectfully submit that the present claims satisfy the requirements of §§ 101 and 112.

For these reasons, Applicants respectfully submit that the instant rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement

The Examiner has also rejected claims 5 to 32 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. In particular, the Examiner alleges that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that Applicants had possession of the claimed invention at the time the application was filed. Office Action, p. 4, lines 16 to 20. Applicants traverse the rejection with respect to all pending claims for the reasons discussed below.

The written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied if one of ordinary skill in the art, reading the specification, would understand that Applicants were in possession of the claimed invention at the time of filing the application.

Applicants respectfully contend that the present claims were sufficiently described in the specification as filed. Furthermore, Applicants have provided many examples of specific

compounds that fall within the presently pending claims. As such, one of skill in the art would have understood that Applicants were in possession of the claimed invention at the time the application was filed.

Furthermore, the Examiner has alleged that the specification does not teach how to use the claimed compounds. Office Action, p. 4, lines 21 to 22. Applicants understand this rejection as resting on the same grounds as the enablement rejection addressed above. As such, Applicants respectfully request that the Examiner consider the arguments addressing the enablement rejection found in the previous section.

Applicants respectfully submit that they have overcome this rejection and ask that it be withdrawn.

Last, Applicants hereby petition for any required extension of time. Please charge all required fees to Deposit Account No. 500329.

Respectfully submitted,

Date: **November 30, 2005**

Jeffrey H. Tidwell
Attorney for Applicants
Registration No. 47,995

Agouron Pharmaceuticals, Inc./A Pfizer Company
Patent Department
10777 Science Center Drive
San Diego, California 92121
Phone: (858) 638-3877
Fax: (858) 678-8233